

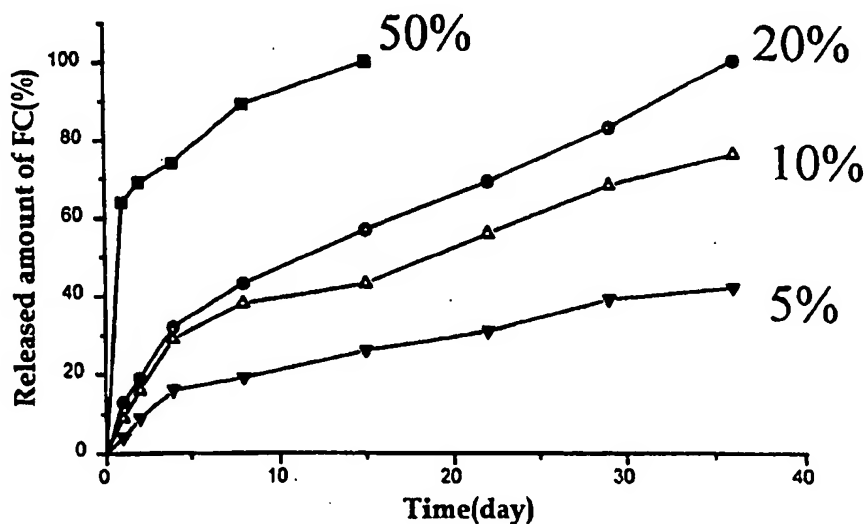


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/445, 9/00, 9/14, 9/22, 9/56, 9/70, 47/30		A1	(11) International Publication Number: WO 99/36071
			(43) International Publication Date: 22 July 1999 (22.07.99)
(21) International Application Number: PCT/KR99/00033		(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).	
(22) International Filing Date: 19 January 1999 (19.01.99)		Published With international search report.	
(30) Priority Data: 1998/1442 19 January 1998 (19.01.98) KR			
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(54) Title: BIODEGRADABLE POLYMER MATRICES FOR SUSTAINED DELIVERY OF ANESTHETICS



(57) Abstract

The invention herein relates to biodegradable polymer matrices for sustained delivery of anesthetics or more particularly, to a sustained release anesthetic preparation where fentanyl-based anesthetic is incorporated into a biodegradable polymer.

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BIODEGRADABLE POLYMER MATRICES FOR SUSTAINED DELIVERY OF ANESTHETICS

5 BACKGROUND OF THE INVENTION

Field of the Invention

The invention herein relates to biodegradable polymer matrices for sustained delivery of anesthetics or more particularly, to the sustained release of an anesthetic preparation in such a manner that anesthetics, widely applicable as pain-killers for the management of various forms of chronic pain, such as pre- and post-operative pain, or the pain associated with many types of cancer, are incorporated into the biodegradable polymer which in turn is formulated into a micro-particles type. As a result, the sustained release delivery of drug in the constant level of concentration is achieved. Through this formulation, the biodegradable polymer matrices of the invention herein is capable of 1) providing a localized method in which anesthetic may be administered to the affected or pain sites only, 2) eliminating the toxicity associated with over-dosage, and 3) avoiding various side reactions.

20 Description of the Related Art

In order to relieve pain in the target area of pre-operative or chronic cancer patients, a local anesthetics is clinically used which is administered through an injection needle or syringe to a wounded or affected site over a period of a certain time.

25 This required repeated administration where the pain is to be blocked over a period of greater than one day, either as a bolus or through an indwelling catheter connected to an infusion pump. These methods have the disadvantage of potentially causing irreversible damage to nerve or surrounding tissues due to fluctuations in concentration and high levels of

anesthetic. In addition, an anesthetic administered by these methods has encountered the following shortcomings, i.e., a) all the targeted and surrounding areas should be anesthetized for the purposes of anesthesia at the affected and pain sites, and b) anesthetic delivered in the form of pulse instead of zero-order kinetics may aggravate adverse reactions due to over-dosage. In all cases, therefore, analgesia rarely lasts for longer than six to twelve hours, more typically six hours. Also, in the case of a pump, the pump tubes and infusion lines are difficult to position and secure, the patient has limited, encumbered mobility and, when the patient is a small child or physically impaired, the applicable scope of the pump is extremely limited.

Anesthetics are administered in a variety of ways, including by injections, topical administration, oral administration, and sustained release devices. Injection administration has been widely used for systemic anesthesia. Further, the sustained release devices system can potentially provide for a sustained, controlled, constant localized release for a longer period of time than that which can be achieved by injection or topical administration.

Such sustained release preparations have been intensively studied in the middle of 1980. These preparations typically consist of a polymeric matrix liposome from which drug is released by diffusion and/or degradation of the polymer matrix. Hence, the release pattern of drug is principally determined by the polymer matrix, as well as by the percent loading, method of manufacture, micro-droplets, and film. A major advantage of sustained release preparations using a biodegradable polymer is that they do not require the surgical removal of the drug depleted device. In fact, such preparations are slowly degraded and absorbed by the patient's body, and ultimately disposed of along with other soluble metabolic waste products.

As another case of using the biodegradable polymer for anesthetic, methoxyflurane has been incorporated into liposomes and lecithin micro-

droplets (Haynes et al., *Anesthesiology*, 63, 490-499, 1985). To date, lecithin and liposome preparations have failed to provide sustained release of more 3 days since liposomes and lecithin micro-droplets degrade or are phagocytized rapidly, in a matter of hours. Other lipid-based devices, formed in combination
5 with polymer, for sustained release of localized anesthetic are described in U.S. Patent No. 5,188,837, but these devices have encountered the limited scope of application due to the aforementioned problems.

In addition, local anesthetics for sustained release have been prepared by incorporating bupivacaine into polylactic acid micro-droplets, as described
10 by Wakiyama et al., *Chem. Pharm. Bull.*, 30, 3719-3727(1982). In contrast to the lipid-based materials, the polylactic acid micro-droplets take over a year to degrade and cause localized inflammation. Further, Berde et al., 1990 Annual Meeting, *Am. Soc. Anesthesiologists*, 73: A776 (Sept. 1990), reported a method of manufacturing a sustained release preparation formed of a polyanhydrides
15 polymer matrix, into which dibucaine was incorporated by compression molding. This sustained release preparation, however, had several drawbacks. For example, the preparation displayed bulk erosion, causing a rapid initial release of drug. In addition, the preparation often generated an infection or a capsule of serous material or fibrin, which is particularly a
20 problem when located adjacent to nerve.

For the purposes of localized anesthesia, there has been a report of a method of manufacturing biodegradable micro-droplets where bupivacaine was incorporated into a polylactic acid-glycolic acid copolymer [WO 95/09613]. However, these micro-droplets having low initial drug loading is responsible
25 for the significant drug loss, and the slow release profile thereof does not last for more than 3 days. In the similar cases as above, etidocaine, tetracaine, lidocaine, xylocaine and the chlorides thereof have been used in combination with the biodegradable polymer for the purposes of sustained release [WO

94/05265], but these compounds were plagued with the same aforementioned problems. Thus, there is a great need for the improvement thereto.

Further, sustained release anesthetics such as benzocaine and procaine have been incorporated into polymeric prodrug, as described by M. Kolli et al.,
5 Int. J. Pharm., 81, 103-110(1992), but the use of such anesthetics have not been recommended due to poor potency as compared to the target level.

In addition, morphine preparations for oral administration were commercialized in MST Continus™. These preparations contain a hydrophilic granule system within hydrophobic matrix [J. Alvarez-Fueutes et al., Int. J. Pharm., 139, 237-241(1996)]. According to this method, micro-droplets were
10 made available by incorporating morphine into the biodegradable polymer for the sustained release property of drug, but such sustained release preparations were capable of providing the sustained release effects for only a short period of time (about 48 hours), as described by E. Polard et al., Int. J. Pharm., 134, 37-
15 46, (1996).

Meanwhile, the above cited anesthetics (e.g., methoxyflurane, bupivacaine, dibucaine, benzocaine, procaine, morphine, etidocaine, tetracaine, lidocaine, xylocaine, xylazine, and ketamine) have disadvantages in that a) anesthesia is insufficient, and b) some adverse reactions such as hypertension,
20 hypotension, nausea, vomiting, pruritus, erythema and headache may occur. To overcome the problems of these conventional anesthetics, U.S. Patent No. 3,141,823 (1964) has been directed to synthetic fentanyl-based anesthetics, which are approximately 80~300 times more potent than morphine and in particular, 7.8×10^3 times more potent than carfentanil but with far less side
25 reactions as compared to the conventional anesthetics (R. R. Watson, Drugs of Abuse and Neurobiology, 69-83, 1992, CRC, Boca Raton, FL). However, such drug is mainly administered by injection, and Duragesic™ (Alza Co., USA) only has been on the market as a sustained release drug for transdermal

delivery. Therefore, such injectable form cannot control the dosage amount via epidermal means in an accurate manner, and the majority of patients have complained about acute pain due to far less anesthetic effects.

5 SUMMARY OF THE INVENTION

In order to solve the aforementioned problems, the inventor et al. have conducted intensive studies for the application of the method of the sustained release drug using the biodegradable polymer to the sustained release Japanese encephalitis vaccine (Korean Patent Application No. 96-29789, July 23, 1996),
10 and sustained release AZT preparation (Korean Patent Application No. 97-31100, July 4, 1997). In the midst of this research, a sustained release preparation was devised by specifying the nature and contents of the particular biodegradable polymer which is more suitable to the fentanyl-based anesthetic. In particular, the inventor et al. have discovered that when anesthetic,
15 incorporated into the biodegradable polymer, is administered to the human body, a polymer is biodegraded over a certain period of time and anesthetic and drug is released in a sustained and continuous fashion. This release pattern may control the concentration of anesthetic in the plasma in a constant and minimal manner while effectuating the sustained release of drug at the
20 local site for pain relief. Using the aforementioned factors, the invention herein has been so devised.

Therefore, an object of this invention is to provide biodegradable polymer matrices for sustained delivery of anesthetics during anesthetics administration in such a manner that adverse reactions associated with over or
25 under-dosage may be prevented and a complete zero-order release may be obtained without any initial bulk erosion induced by the conventional manufacturing methods.

Brief Description of the Drawings

Fig. 1 is a graph showing the sustained release in accordance with the initial drug loading of fentanyl citrate biodegradable polymer micro-droplets;

Fig. 2 is a graph showing the sustained release in accordance with the initial drug loading of fentanyl citrate biodegradable polymer pellets; and

Fig. 3 is a graph showing the sustained release in accordance with the initial drug loading of lofentanyl biodegradable polymer film.

Detailed Description of Preferred Embodiments

This invention is characterized by a sustained release anaesthetic preparation where fentanyl-based anesthetic is incorporated into a biodegradable polymer.

This invention is explained in more detail as set forth hereunder. This invention is characterized by a novel sustained release anaesthetic preparation with the following advantages, i.e., a) fentanyl-based anesthetic drug is evenly incorporated into the biodegradable polymer, b) it is possible to tailor a system consisting of certain-size micro-particles to deliver the amount of anesthetic according to the severity of affected site without initial bulk erosion, and c) it does not require the surgical removal of the depleted drug since it is slowly degraded in the patient's body.

First of all, as for anesthetics compatible under the present invention, one or more fentanyl-based anesthetic may be selected from the group consisting of fentanyl, benzylfentanyl, alpha-methylfentanyl, ρ -fluorofentanyl, 3-methylfentanyl, acetyl-alpha-methylfentanyl, alpha-methylacrylfentanyl, alpha-methylthiofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, 3-methylthiofentanyl, thiofentanyl, thenylfentanyl, sufentanil, carfentanil, llofentanil and alfentanil, or the salts, bromides, acetates, citrates and sulfates thereof. Being different from the conventional ones, the above

anesthetics posed difficulty as to the sustained release preparations for long-term therapeutic action due to problems in incorporating anesthetic into the biodegradable polymer. However, the invention herein has succeeded in overcoming the aforementioned problems by introducing a novel
5 biodegradable polymer as described hereunder.

The present invention is characterized in that a specific biodegradable polymer is selected as a novel clathrate for anesthetics as above, and the particle size and molecular weight of micro-droplets thereof are limited so as to attain the zero-order profile for a prolonged period of time. Further, the
10 biodegradable polymer selected from this invention is harmless in the body and can be degraded in the desired period of time.

The biodegradable polymer used as an anesthetic clathrate of said invention includes albumin, collagen, gelatin, fibrinogen, casein, fibrin, hemoglobin, transferrin, chitin, chitosan, hyaluronic acid, heparin, chondroitin,
15 keratinsulfate, alginic acid, starch, dextrin, dextran, polylactic acid, polyglycolic acid, lactic acid-glycolic acid copolymer, polyhydroxybutylic acid, polycaprolactone, polyanhydrides and polyalkylcyanoacrylate. Through the application of these materials, the problems induced by the conventional biodegradable polymer clathrate (e.g., accurate adjustment in the
20 biodegradable period of time, etc.) may be resolved.

In particular, it is preferred that the molecular weight of the biodegradable polymer be 5,000~1,000,000 g/mole. If the molecular weight is less than 5,000, the expected effect of sustained release preparation cannot be obtained due to the extremely short biodegradation period. However, in case
25 of exceeding 1,000,000 in the molecular weight, the biodegradation period will be excessively extended.

The sustained release anesthetic preparations can be used in the form of slabs, beads, pellets, fine powders, micro-droplets, micro-capsules, films,

and pastes.

The sustained release anesthetic preparation of the present invention may be manufactured in the form of micro-particles based on the biodegradable polymer by a commonly available method, and this manufacturing method is explained in more detail as set forth hereunder. The method of preparing the sustained release anesthetic preparation includes an inter-emulsifying solvent evaporation method (inter-emulsifying solvent evaporation of O/W, W/O, O/O and W/O/W), phase separation method based on the non-solvent addition or solvent separation method, interfacial polymerization method, and spray-drying method. Among these methods, it is preferable to use the inter-emulsifying solvent evaporation method.

As one preferred embodiment of the present invention designed to prepare the sustained release preparations of micro-droplets incorporated into anesthetic, the inter-emulsifying solvent evaporation method is explained in more detail as set forth hereunder.

The biodegradable polymer is dissolved in an organic solvent to yield a 0.5~30 W/V% solution. In certain preferred embodiment of the present invention, one or more solvents may be selected from the group consisting of methylene chloride, acetonitrile, chloroform, dioxane, formamide and acetylamide.

To the biodegradable polymer of 30~99.99% by weight, anesthetic is added in the amount of 0.01~70% by weight. Thereafter, the mixture is prepared in the form of solution or in the dispersed state by a sonication mixer or homogenizer. If the content of anesthetic is less than 0.01% by weight, the manifestation of drug will not be made available due to extremely low concentration of anesthetic. However, if the content of anesthetic exceeds 30% by weight, the excessive initial release of drug may produce some adverse reactions, let alone higher production costs.

The solution is added to other oil phase where an emulsifier is dissolved in the concentration of 0.01~10 W/V%. In order to remove an organic solvent, the resulting solution is stirred at 10~50°C at 300~20,000 rpm for 1~24 hours. One or more emulsifier may be selected from the group consisting of polyvinyl alcohol, sodium dodecyl sulfate and polyethylene oxide, including currently marketed materials such as SpanTM, TweenTM, BrijTM, and PluronicTM. Further, since the stirring rate and time is the most important parameters in modulating the size of micro-particles, the above parameters should be accordingly adjusted if deemed necessary.

In the final step, the micro-particles containing anesthetic within the solution is recovered by an ultracentrifuge and filter. Thereafter, the micro-particles are dried at room temperature and lyophilized to obtain the final micro-particles.

Hence, the reason for having the size of final micro-particles by 0.1 μ m ~20mm in diameter is as follows: If the size of micro-particles is less than 0.1 μ m, the sustained release profile of drug (e.g., initial burst effect, etc.) cannot be properly controlled, but in case of 20mm or more, there are some drawbacks in human administration.

The adjustment of size in the micro-particles, which has been known to those skilled in the art, may be available by the following parameters: stirring rate in mixing an emulsifying solution derived from the anesthetic and biodegradable polymer, and other oil phase where an emulsifier is dispersed; molecular weight of the biodegradable polymer used; and concentration of the biodegradable polymer on solvent.

Further, sustained release anesthetic preparation of the present inventions may be manufactured in the form of pellets based on the biodegradable polymer and some commonly available method, and the manufacturing method thereof is explained in more detail as set forth

hereunder.

To the pulverized or powdered biodegradable polymer of 30~99.99% by weight, anesthetic is added in an amount of 0.01~70% by weight and then, the mixture is homogeneously blended by a commonly used mixer. The resulting solution is melted for injection at 150~250°C via a mould having 1mm in diameter using a polymer-processing kneeder or an injector equipped with screw. The injected material is cooled in air and cut by 1mm in length to obtain the sustained release local anesthetic in the final form of pellets. Hence, it is preferred to set the size of final pellets by 50 μ m~10mm in diameter and 50 μ m~10mm in length since the pellets are prepared in the same manner as the micro-particles.

The sustained release anesthetic preparation of the present invention may be manufactured in the form of film based on the biodegradable polymer by a commonly available method, and the manufacturing method thereof is explained in more detail as set forth hereunder.

The biodegradable polymer is dissolved in an organic solvent to yield a 0.5~30 W/V% solution. At this point, one or more solvents may be selected from the group consisting of methylene chloride, acetonitrile, chloroform, dioxane, formamide and acetylamine. To the biodegradable polymer of 30~99.99% by weight, anesthetic is added in the amount of 90~0.01% by weight. Thereafter, the mixture may be prepared in the form of solution or in the dispersed state by a sonication mixer or homogenizer.

For the purposes of producing a film having 0.5 μ m~10mm in thickness, the solution is placed into a film machine equipped with Doctor's knife, impregnated in a non-solvent and dried off. By cutting into an appropriate size, the sustained release local anesthetic may be produced in the form of films.

The sustained release anesthetic preparation of the present invention

may be manufactured in the form of pastes based on the biodegradable polymer by a commonly available method, and the manufacturing method thereof is explained in more detail as set forth hereunder.

The biodegradable polymer is dissolved in an organic solvent to yield a
5 0.5~80 W/V% pastes. As far as the applicable solvents are concerned, organic solvents used for the preparation of micro-droplets and film may be also employed. At this point, the anesthetic is added to the biodegradable polymer in the amount of 0.01~70% by weight. In order to homogeneously disperse the drug in the pastes, a sonication mixer or homogenizer is used.
10 The pastes may be directly injected to the affected site via syringe. The sustained release local preparations in the form of pastes may be prepared by a generally applicable procedure known to those skilled in the art. Hence, a biodegradable period and sustained release pattern of anesthetic may be controlled by the following parameters: molecular weight of the biodegradable
15 polymer used, concentration of the biodegradable polymer on solvent, and concentration of emulsifier when an emulsifying solution derived from the anesthetic and biodegradable polymer is prepared.

In the preferred method of administration according to the present invention, micro-droplets, fine powder, and micro-capsule may be
20 subcutaneously injected by a proper gauge at the target site of pain relief. Alternatively, the films, slabs and beads may be surgically implanted at the site. The pellets may be injected through a trochar, and the pastes may be administered subcutaneously.

The following examples illustrate various aspects of the invention
25 herein but should not be construed to limit the claims in any manner whatsoever.

Example 1

Monomers of lactic acid and glycolic acid were mixed in the weight ratio of 75:25. Then, the mixture was under thermal polymerization at 170°C at 100 rpm for 40 hours to yield a copolymer. The molecular weight of the copolymer (hereafter referred to as "PLGA75"), so dried, was 25,000 on gel permeation chromatography.

0.4g of PLGA75, so produced, was evenly dissolved in 8ml of methylene chloride. Then, 0.05g (initial drug-loading content: 5%, 10%, 20%, and 50%, respectively) of fentanyl citrate(FC) was added to said mixture via an ultrasonicator (40W) for 30 seconds to yield a solution. The solution was rapidly poured into a mineral oil phase where approximately 0.05 W/V% of Span 80 was dissolved and centrifuged at 250 rpm. In order to remove methylene chloride contained in the solution, the resulting solution was stirred at 25°C at 250 rpm for 3 hours.

Then, the solution was further centrifuged at 3000 rpm for 15 minutes to collect the FC/PLGA75 micro-particles contained in the solution. These micro-particles, so collected, was washed with hexane, dried and measured by a Coulter counter. The FC/PLGA75 micro-particles were $45 \pm 7 \mu\text{m}$ in size.

The drug release of these biodegradable micro-particles was measured in PBS solution at 37°C, as shown in Fig. 1.

Example 2

0.8g of polyhydroxybutylic acid (PHB) having the molecular weight of 15,000 was dissolved in 8ml of chloroform. Then, 0.2g of benzylfentanyl (BF) was added to said mixture via an ultrasonicator (40W) for 30 to yield a solution. The following reactions were carried out in the same procedure as described in the Example 1.

These BF/PHB micro-particles, so collected, were measured by the

same Coulter counter as described in the Example 1. The BF/PHB micro-particles were $270 \pm 35 \mu\text{m}$ in size.

Example 3

5 1.2g of polycaprolactone (PCL) having the molecular weight of 27,000 was dissolved in 8ml of dioxane. Then, 0.3g of sufentanil (SF) was added to the mixture to produce a solution via an ultrasonicator (40W) to produce a solution.

 In the same procedure as described in the Example 1, the final micro-
10 particles was obtained with the SF/PCL micro-particles of $73 \pm 20 \mu\text{m}$.

Example 4

 1.0 W/V% solution of alginic acid containing 20% thiofentanyl (TF) was sprayed to 1.5 W/V% of calcium chloride solution by an air-atomizer
15 (Turbotak Co.), crosslinked and coated with polylysine (PL).

 In the same procedure as described in the Example 1, the final micro-particles were so obtained. The TF/PL micro-particles were $47 \pm 13 \mu\text{m}$ in size.

Example 5

20 Monomers of lactic acid and glycolic acid were mixed in the weight ratio of 50:50. Then, the mixture was under thermal polymerization at 165°C at 150 rpm for 24 hours to produce a copolymer. The molecular weight of the copolymer (hereinafter referred to as "PLGA50"), so prepared, was 12,000 on gel permeation chromatography.

25 0.5g of PLGA50 was evenly dissolved in 6ml of dioxane. Then, 0.1g of beta-hydroxyfentanyl (HF) was added to the mixture. The micro-particles containing the HF was obtained under the same procedure as described in the Example 1. The HF/PLGA50 micro-particles were $87 \pm 16 \mu\text{m}$ in size.

Example 6

0.1mg of fentanyl was added to 10ml of aqueous solution containing respective concentration of 0.5% glucose, 70% dextran and 0.05% citric acid. Then, the mixture was stirred the mixture at 900 rpm. 2ml of
5 hexylisocynoacrylate, a monomer, was added to the mixture in a reactor for 5 hours, whereby the micro-particles having $2.3 \pm 0.7 \mu\text{m}$ size were produced.

Example 7

200g of the PLGA 75, so formed from the Example 1, was prepared in
10 the form of powder and mixed completely with the addition of 1g of FC (initial drug-loading content; 1%, 2.5%, 5% and 10%). Then, the mixture was injected by molding at 170°C using Brabender (Plasti-Corder REO6 type) equipped with die having 0.5mm in diameter and cut in a length of 0.5mm to produce the final pellets. The FC drug release of these biodegradable pellets was
15 measured in PBS solution at 37°C, as shown in Fig. 2.

Example 8

6g of PLGA75, so formed from the Example 1, was evenly dissolved in 8g of dimethylsulfoxide and mixed with 0.5g of the FC. At this point, for the
20 purposes of complete mixing, 0.05 W/V% of Span 80 was added to the mixture, and a paste having a viscosity of 230cp was produced using a homogenizer.

Example 9

50g of PLGA 50, so formed from the Example 5, was evenly dissolved
25 in 100ml of methylene chloride and dispersed uniformly with the addition of 20g of alfentanil (AF) in 0.05 W/V% of Twin.

The mixture was placed in an oven at 75°C for 24 hours in order to evaporate methylene chloride, whereby a AF-contained mass of PLGA 50 was

obtained. Such mass was grounded into powder by a mill, and the powder of less than 50 μm was obtained using a molecular sieve of 50 μm .

Example 10

5 0.8g of polyanhydrides having the molecular weight of 25,000g/mole was dissolved in 80ml of dioxane. A mixture of 0.02g of lofentanyl(LF) (initial drug-loading content of 5%, 10%, 20% and 50%) and 0.001g of Span 80 was added to the solution, thus producing the desired solution by using an ultrasonicator (40W) for 30 seconds. Then, the films having the final thickness
10 of 0.7mm were prepared by a cutter equipped with Doctor's knife. The LF drug release of these biodegradable films was measured in PBS solution at 37°C, as shown in Fig. 3.

As shown in the Fig. 1, the sustained release anesthetic preparation according to the examples of the present invention displayed a nearly zero-
15 order release from one day to approximately 2 months, which is an ideal drug of choice for the management of various forms of chronic pain, such as pre- and post-operative pain, or the pain associated with many types of cancer.

Therefore, the sustained release anesthetics according to the present invention have the following advantages as compared to the prior arts: a) by
20 selecting a biodegradable polymer suitable to anesthetic, the toxicity associated with over-dosage and various adverse reactions, e.g., nausea, vomiting, headache, hypertension, hypotension, pruritus, and erythema, may be avoided; b) in accordance with the degree of anesthesia of a patient at the localized site, both anesthetic and biodegradable polymer preparations can be tailored
25 beforehand and then, depending on the patient's drug requirement for the amount of drug may be released via the desired local form or in the desired administration period of time; c) compared to the conventional sustained release preparations, the sustained release preparations of the invention herein

may enhance the initial drug-loading content, thus gaining more prolonged anesthetic effects; and,

d) by means of a biodegradable polymer used for drug delivery which may be degraded and absorbed in the body, the fentanyl-based active ingredient with
5 remarkable therapeutic effects can be given to the patients through various administration methods other than orally.

Further, the sustained release anesthetic preparations according to the invention herein may be applicable to other drugs, thus paving the way to be a wide utilization in the related industry.

CLAIMS

What is claimed is:

1. Biodegradable polymer matrices for sustained delivery of anesthetics,
5 wherein fentanyl-based anesthetics are incorporated into the biodegradable polymers.
2. Biodegradable polymer matrices for sustained delivery of anesthetics according to claim 1, wherein said matrices comprise 30 ~ 99.99 weight
10 percentage of biodegradable polymers and 0.01~70 weight percentage of fentanyl-based anesthetics.
3. Biodegradable polymer matrices for sustained delivery of anesthetics according to claim 1 or 2, wherein one or more fentanyl-based anesthetics are
15 selected from the group consisting of fentanyl, benzylfentanyl, alpha-methylfentanyl, *p*-fluorofentanyl, 3-methylfentanyl, acetyl-alpha-methylfentanyl, alpha-methylacrylfentanyl, alpha-methylthiofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, 3-methylthiofentanyl, thiofentanyl, thenylfentanyl, sufentanil, carfentanil, lofentanyl and alfentanil,
20 or the salts, bromides, acetates, citrates and sulfates thereof.
4. Biodegradable polymer matrices for sustained delivery of anesthetics according to claim 1 or 2, wherein one or more biodegradable polymers are selected from the group consisting of albumin, collagen, gelatin, fibrinogen,
25 casein, fibrin, hemoglobin, transferrin, chitin, chitosan, hyaluronic acid, heparin, chondroitin, keratinsulfate, alginic acid, starch, dextrin, dextran, polylactic acid, polyglycolic acid, lactic acid-glycolic acid copolymer, Polyhydroxybutylic acid, polycaprolactone, polyanhydrides and

polyalkylcyanoacrylate.

- 5 5. Biodegradable polymer matrices for sustained delivery of anesthetics according to claim 1, wherein said matrices are in the forms of slabs, beads, pellets, fine powders, micro-droplets, micro-capsules, films, and pastes.
6. Biodegradable polymer matrices for sustained delivery of anesthetics according to claim 1, wherein said matrices are micro-particles of $0.1\text{ }\mu\text{m}$ ~ $20\text{ }\mu\text{m}$ in diameter.

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FIGURE

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Fig. 1

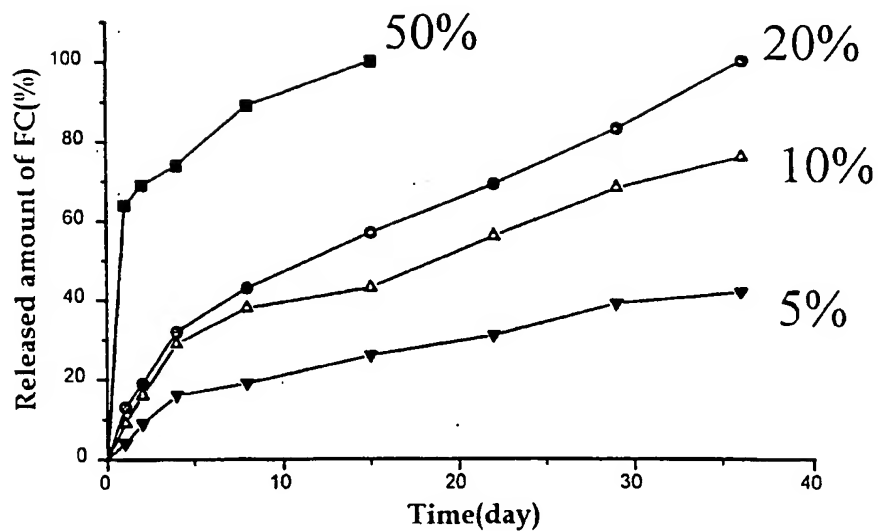
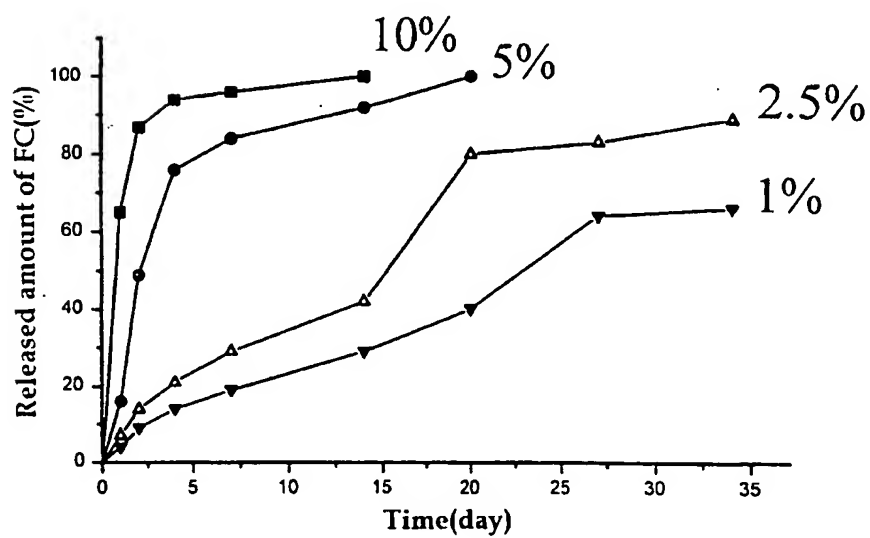


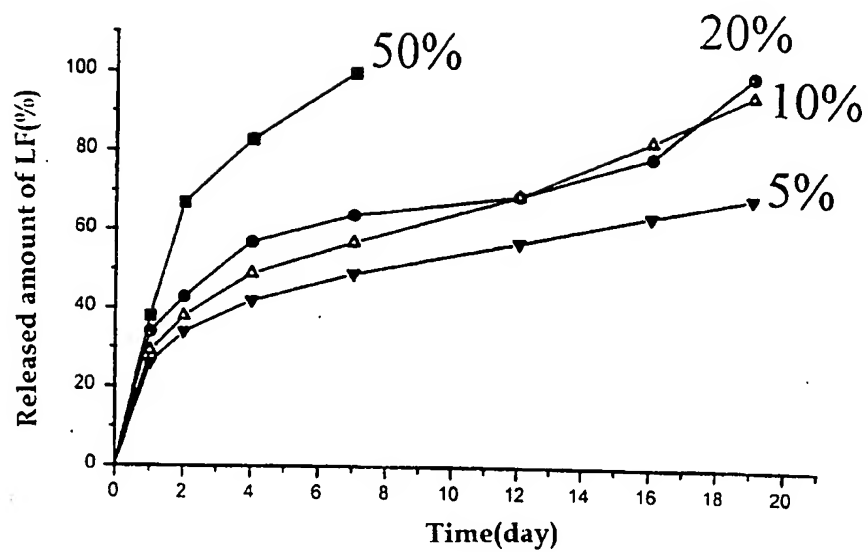
Fig. 2



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Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00033

A. CLASSIFICATION OF SUBJECT MATTER		
IPC ⁶ : A 61 K 31/445, 9/00, 9/14, 9/22, 9/56, 9/70, 47/30		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC ⁶ : A 61 K 31/445, 9/00		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
CAS (QUESTEL)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/01 807 A1 (ALZA CORPORATION) 04 February 1993 (04.02.93), claims 1,19,27,30,31; page 19, lines 13-17, examples I,III; page 13, line 32 - page 14, line 2; page 15, lines 18-23.	1-5
X	GB 2 239 803 A (ELAN CORPORATION PLC) 17 July 1991 (17.07.91), claims 19,20,25,26; page 9, line 3 - page 10, line 11; page 11, lines 15-25.	1-5
Y	FR 2 070 153 A (E.I. DU PONT DE NEMOURS AND COMPANY) 10 September 1971 (10.09.71), claims 1,5-9; page 3, lines 3-13.	1-6
Y	EP 0 556 158 A1 (CIBA-GEIGY AG) 18 August 1993 (18.08.93), claim 9; column 4, lines 13-16,21-22.	1-6
A	WO 89/03 678 A1 (STOLLE RESEARCH & DEVELOPMENT CORPORATION) 05 May 1989 (05.05.89), claims 1,4,5,14,15,18; page 3, lines 3-27; page 13, lines 5-8.	1,2,4-6
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: „A“ document defining the general state of the art which is not considered to be of particular relevance „E“ earlier application or patent but published on or after the international filing date „L“ document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) „O“ document referring to an oral disclosure, use, exhibition or other means „P“ document published prior to the international filing date but later than the priority date claimed „T“ later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention „X“ document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone „Y“ document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art „&“ document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
01 April 1999 (01.04.99)		27 April 1999 (27.04.99)
Name and mailing address of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535		Authorized officer Mazzucco Telephone No. 1/53424/437

INTERNATIONAL SEARCH REPORT

International application No.

PCT/KR 99/00033

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 246 514 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES) 05 February 1992 (05.02.92), abstract; claims 1,8,10,14,16; page 5, lines 11-19; page 6, lines 14-28.	1,2,4-6
A	WO 94/10 987 A1 (PHARMETRIX CORPORATION) 26 May 1994 (26.05.94), claims 1,7,8,13,17,21-23; example 13.	1-3,5
A	EP 0 330 180 A1 (BIOMATERIALS UNIVERSE, INC.) 30 August 1989 (30.08.89), abstract; claims 1-4.	1,2,6
A	US 5 271 945 A (YOSHIOKA T. et al.) 21 December 1993 (21.12.93), column 1, line 45 - column 2, line 2; column 4, lines 40-57; column 6, lines 40-47,63-67; column 7, line 53 - column 8, line 3.	1,2,4-6
A	WO 95/09 613 A1 (CHASIN M. et al.) 13 April 1995 (13.04.95), abstract; claims 1,4.	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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